BIOABSORBABLE POLYMERS

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SCOPE

Addressed in this article are polymers that, because of their current and future applications, require that they interface with living tissues for predetermined periods. Obviously, the physical presence of these polymers in the biological environment must be transient, and their physicochemical properties are expected to meet the in-use requirements and allow their transport or clearance from the application site when the intended efficacy is achieved. The transport or clearance of those polymers while in contact with tissues is termed *bioabsorption*. Hence, the term *bioabsorbable polymers* is used to denote all transient polymeric materials, regardless of their chemical type, origin, and mode of clearance or absorption from the application site. Bioabsorbable polymers can be derived from naturally occurring polysaccharides and proteins, totally synthetic polymers, or combinations of natural and synthetic components, and they may be transported from the application site through the following: 1) dissolution followed by diffusion, with or without a simple ion-exchange process to achieve solubility; 2) chemical chain dissociation of insoluble materials and their conversion to small particles suitable for phagocytosis or to soluble chain fragments that may also be metabolizable; or 3) enzymatic dissociation of the insoluble polymers to soluble moieties. Major types of bioabsorbable polymers and possible modes of bioabsorption are discussed in the next section. This section also provides some technological details on bioabsorbable materials based on soluble or solubilizable chain molecules and on polymers that can be converted to soluble forms without undergoing scission of any covalent bonds. Then an important class of polymers that undergo bioabsorption through depolymerization and chain scission is discussed. This section also includes a discussion on the newly available absorbable gel-former liquids. Throughout both sections, brief discussions relevant to the application of bioabsorbable polymers address topics such as polymer processing and applications.

MAJOR TYPES OF BIOABSORBABLE POLYMERS AND POSSIBLE MODES OF BIOABSORPTION

The chemical structure of the chain molecules is the major factor that determines the mode of bioabsorption. About two decades ago, most bioabsorbable polymers were natural polymers or derivatives thereof. Scientific interest in totally synthetic bioabsorbable polymers has grown considerably since the early seventies because of their relatively low tissue reaction and because of their more predictable in vitro and in vivo properties as compared with the natural materials. Bioabsorbable polymers can be classified into three major groups: soluble, solubilizable, and depolymerizable. The structural features and possible mode of bioabsorption of these polymers are outlined as follows.

Soluble Polymers

Soluble chain molecules are usually water-soluble, natural, modified natural, or synthetic materials. These polymers are characterized by having hydrogen-bonding, polar groups that are responsible for their water-solubility and their transport in the biologic environment. The solubility of these polymers is dependent, to a great extent, upon the type of these polar groups (hydroxyl, carboxyl, amido, or amino) and the location in the chain (as part of the main chain or side groups). Molecular weight (1) and branching of the polymer chain also play a key role in determining the polymer solubility. Examples of water-soluble polymers and the type of polar groups they carry are given in Tables 1 and 2.

Some of the most important water-soluble polymers belong to the family of polysaccharides. Soluble polysaccharides were discussed in a review by Franz (2) on polysaccharides in pharmaceutical formulations. Due to their industrial importance, key characteristics and typical applications of those polysaccharides are listed in Table 3. In addition to those noted in Table 3, the oxidation of cellulose (to convert 16–24% of its primary hydroxyl groups to carboxyl groups) produces oxidized cellulose, a

Table 1 Types of polar groups in typical examples of water soluble polymers

Polar group	Natural polymers	Modified natural polymers	Synthetic polymers
–OH	Dextran and alginic acid	Hydroxyethyl cellulose and hydroxypropyl cellulose	Polyvinyl alcohol, polyhydroxyethyl methacrylate, and low-molecular-weight polyethylene oxide
–C–O–C	Dextran	Hydroxyethyl cellulose and hydroxypropyl cellulose	Polyethylene oxide and copolymers of ethylene and propylene oxide
–COOH	Alginic acid	Carboxymethyl cellulose	Polyacrylic acid
$-CO-NH_2$	—	—	Polyacrylamide
–CO–NH–	—	Gelatin	Polylysine
$-C-NH_2$	—	—	Polylysine

fibrous white powder. It is used as a bioabsorbable hemostatic agent. The bioabsorption may be partly attributed to solubilization through the carboxylate moieties.

Blends of different polysaccharides and plasticizers are commonly used in pharmaceutical formulations, particularly those geared for controlled release. Due to its importance, the physical compatibility of these blends was examined by a number of investigators. Sakellariou and associates (3) studied the polymer–polymer interaction in blends of ethyl cellulose with a few cellulose derivatives (hydroxypropyl methyl-cellulose, hydroxypropyl cellulose, hydropropyl methylcellulose phthalate, and cellulose acetate phthalate) and polyethylene glycol-6000. They noted that hydroxypropyl methylcellulose phthalate and cellulose acetate phthalate exhibited initial interaction and mutual dispersion owing to the presence of the phthalyl groups.

The growing interest in new or modified water-soluble polymers or combinations thereof to meet the needs of contemporary pharmaceutic technology is illustrated by a few of the recent studies outlined below. McCormick et al. (4) have relied on copolymerization as an effective means to modify water-soluble polymers, as illustrated in a recent communication. The effect of alkyl side groups on the properties of polyelectrolytes was examined earlier by Dubin and Strauss (5, 6). Pantar and Rao (7), who were also interested in developing polyacrylamide (PAAm) having enhanced dissolution rates, noted the following: 1) the rate of dissolution of this polymer increased when it is prepared in the presence of polyethylene glycols (PEG) 200 and 400; 2) heterogeneous PAAms were found to have occluded the PEG; and 3) incorporation of PEG decreased with the increase in its molecular weight. Gelation and properties of hydrogels based on water-soluble polymers remain important areas, as stressed in a review by Ross-Murphy and McEvoy (8). The gamma ray-induced cross-linking of PAAm with a dose of over 50 kg produces hydrogels that absorb water by 1000–1500 wt% (9). Barbucci et al. (10) synthesized new polymers with amido and amino groups in the side chains and demonstrated the importance of hydrophobic interaction on the protonation of these polymers leading to their solubilization. Association of water-soluble polymers and formation of hetero-pairs by intermolecular complex formation have been the subject of early investigations and hold great promise for future research (5, 6, 11–15).

A review by Drobnik and Rypàcek (16) summarized key findings and some theories on the fate of water-soluble polymers in living organisms, using a compartmentalized model to discuss the polymers' pharmacokinetics and their movement across several biologic barrier membranes in an organism. Compartments of this model are characterized by similarity in the mechanism of crossing the biologic barriers. Thus, the plasma circulation is viewed as the central and the only compartment across which the exchange of compounds between remote parts of the body may be accomplished. Intracellular exchanges were associated with a large intracellular compartment entailing all cells in the body. The authors discussed in some detail the participation of cells of the reticuloendothelial system (RES), kidney tubular epithelium, and liver hepatocytes. The lymph system and interstitium were denoted as important compartments in dealing with synthetic, water-soluble

Table 2 Structural features of typical water-soluble polymers

Name	Class of polymer or source	Solubilizing groups	Other features
Dextran (DXT)	Natural polysaccharide; a bacterial fermentation product	−C−O−C− −C−OH	Substituted pyranose chain sequences
Carboxymethyl cellulose and its alkali metal salts (CMC)	Carboxyalkylated cellulose	−C−O−CH_2COOH −C−O−C	Substituted pyranose chain sequences
Hydroxyethyl cellulose (HEC)	Ethoxylated cellulose	−C−O−CH_2CH_2OH −C−O−C	Substituted pyranose chain sequences
Hydroxypropyl cellulose (HPC)	Propoxylated cellulose	−C−O−CH_2−CHCH3−OH −C−O−C	Substituted pyranose chain sequences
Hydroxypropyl methylcellulose (HPMC)	Methylated HPC	Similar to HPC	Substituted pyranose chain sequences
Poly(β-hydroxyethyl methacrylate) (PHEMA)	Synthetic, by direct polymerization	−CO−O−CH_2CH_2OH	Substituted polyethylene chain
Polyvinyl alcohol (PVA)	Synthetic, hydrolysis product of polyvinylacetate	CH−OH	Substituted polyethylene chain
Polyacrylamide (PA)	Synthetic, by direct polymerization	−$CONH_2$	Substituted polyethylene chain
Polyacrylic acid and its alkali metal salts (PAA)	Synthetic, by direct polymerization	−COOH,−COO−Na^+ and/or −COO−K^+	Substituted polyethylene chain
Polyvinylpyrrolidone (PVP)	Synthetic by direct polymerization	−CO−NH−	Substituted polyethylene chain
Polyethylene oxide (PEO *or* PEG)	Synthetic polyether, by acyclization of ethylene oxide	−CH_2−O−CH_2− −CH_2−OH	Chains carry 2 (OH) end groups, at low and moderate molecular weights
Poly(ethylene oxide-*b*-propylene oxide) (PEO-PPO)	Synthetic block copolymers of ethylene and propylene oxide	−CH_2−O$CHCH_3$− −CH_2−O−CH_2 −CH_2OH −$CHCH_3$−OH	Chains carry up to 2 (OH) end groups, depending on molecular weight
Amylose (soluble starch)	Natural, linear component of starch	−C−O−C −C−OH	Substituted pyranose sequences
Alginic acid and its alkali metal salts	Natural, polysaccharide from seaweed	C−O−C −C−COOH −C−OH	Substituted pyranose sequences of *d*-mannuronic acid
Polylysine	Synthetic	−CO−NH− −C−NH_2	A basic polypeptide
Hyaluronic acid	Natural polysaccharide (e.g., in rooster comb); also a bacterial fermentation product	−C−O−C− −C−OH −C−NHCO−CH_3 −COOH	Substituted pyranose sequences of acetyl Glucosamine and glucuronic acid

Table 3 Soluble polysaccharides: key features and typical applications

Polysaccharide	Structural features	Source and properties	Applications
β–Cyclodextrin	Based on 7 glucopyranose units; the α-form has only 6 units	Amylose derived, cyclic heptasaccharide, capable of forming inclusion complexes of drugs	Inclusion complexes with drugs to mask odor to taste
Methylcellulose	Methylated cellulose with a methoxy content of about 6 – 15%	Solutions are stable at pH 2–12 but coagulate or precipitate in presence of SO_4^{-2} CO_2^{-2} or PO_4^{-3}	Ophthalmic and burn preparations, nose drops and ointments
Cellulose acetate phthalate	Esterified cellulose with about 20 and 35% acetate and phthalate groups, respectively	Free acid form dissolves in organic solvents and only the alkali metal salts are water soluble	Protective coating of tablets, insoluble in stomach but soluble in intestine fluids
Carboxymethyl cellulose	Usually prepared as the carboxylic salt of polycarboxymethyl ether of cellulose	Dispersion of the free acid or its sodium salt is stable at a wide pH range (2–10)	Thickening agent and tablet excipient
Acacia gum	A mixture of structurally related polysaccharides, the main one is based on β-D-galactopyranose residues	Natural plant exudates solutions are stable at pH 2–7 and display relatively low viscosity	Emulsifying or suspending agents, adhesive and binders (in tablets)
Tragacanthin	A complex mixture of polysaccharides containing some galacturonic acid residues	The soluble component of the natural (plant origin) tragacanth gum	Binder (in tablets) and demulcent
Pectin	Made of partly methoxylated 1,4-1inked polygalacturonic acid	At pH 3 pectin forms a thermoreversible gel. It is extracted from citrus peel	Suspending agent, antidiarrheal formulations
Alginic acid	Linear polymer made of β-1, 4-D-mannuronic and l-glucuronic acids	Extracted from brown algae, the polymer sodium salt and not the free acid or calcium salt dissolves in water	Thickening, emulsifying, or gel-forming agent
Agar	Based primarily on galactose sequences	Extracted from red algae	Suspending or emulsifying agent, surgical lubricant, and tablet disintegrant
Galactomannans	Made primarily of a linear mannose chain with galactose side groups	Obtained from the powdered endosperm of certain seeds, guar gum	Thickening agent and tablet binder
Xanthan	Made primarily of linear glucose chain with side chains based on mannose and glucuronic acid residues	A microbial gum made by glucose fermentation, forms viscous pseudoplastic solutions	Emulsifying or suspending agent, particularly in toothpaste and ointments
Dextran	The polysaccharide chain is made primarily (based on the bacterial strain used in fermentation) of glucan units having α-1,6-linkages and fewer α1-2- and 1,3 or 1,4-linkages to give a highly branched structure	A class of exocellular bacterial glucans, commercial dextrans have molecular weights of 40 to 110×10^3. The low molecular wt. dextran (40,000) was reported to clear readily through the kidneys	Blood extender
Hyaluronic acid	Made of acetyl glucosamine and glucuronic acid (partially neutralized to dissolve) sequences	Obtained by the extraction of rooster comb or as a bacterial fermentation product, molecular weight ranges from 0.5 to 3×10^6	Exceptional lubricant for living tissues

(From Ref. 2.)

polymers. Ways in which water-soluble, endogenous and exogenous polymers cross compartmental barriers include transendothelial passage, transport into the lymphatic system, glomerular filtration, tubular secretion, intestinal transport, and biliary transport. In their discussion of compartmental barrier crossing, the authors indicated that water-soluble polymers cannot pass across a lipoprotein membrane by any type of diffusion process without the interruption of the membrane integrity and the development of defects in the cell surface. These defects can be caused by polyelectrolytes or a high concentration of polyethylene glycol. On the other hand, a common process by which polymers can cross a biologic membrane is invagination of the membrane, that is, the formation of a vesicle that buds inward and separates from the membrane. This process, in which the macromolecules enter the cell completely enclosed in a membrane vesicle containing some extracellular fluid, is generally termed *endocytosis*. The authors indicated that vesicle transport seems to be the only way in which synthetic polymers can overcome the lipoprotein membrane barrier. Drobnik and Rypàtcek (16) also discussed the mechanism of storage in cells and elimination via the respiratory system. Although the authors stressed the role of endocytosis in transporting large molecules across biologic barriers, the passive diffusion of soluble polymers of less than 20,000 molecular weight was not excluded. Polymers addressed in this section may or may not undergo limited changes during their residence in the organism. The changes may consist of modifications that have minor effects on their mode of transport, absorption, and eventual elimination from the organism. The chain modification may be associated with hydrolytic reactions, oxidative processes, and/or conjugation (usually through esterification, acylation, or alkylation) but are not expected to introduce major changes in the chain molecular weight or solubility.

Solubilizable Polymers

The second group of bioabsorbable polymers, namely, the solubilizable macromolecules, may be viewed as derivatives of the water-soluble polymers as outlined in

Table 4 Soluble depolymerizable polymers

Name	Class of polymer of source	Solubilizing groups	Other features
Hyaluronic acid (HA) and its alkali metal salts	Natural polysaccharide from rooster comb or obtained as a fermentation product	C–O–C	Substituted pyranose cosequences of glucuronic acid and acetyl glucosamine
		–C–COOH	
		–C–NH–CO–CH_3	
		–C–OH	
Pectin and its alkali metal salts	Natural polysaccharide from citrus fruits	–C–O–C	Substituted pyranose sequences of galacturonic acid
		–C–COOH	
		–C–OH	
Gelatin	A hydrolysis product of collagen (a natural polymer)	Mostly –CO–NH–	Major constituent amino acids are glycine, proline, and hydroxyproline
Protamine (as a sulfate)	Natural polymer from fish eggs	–COHN–	A basic low-molecular-weight protein with arginine as a dominant amino acid constituent
		$-COHN-$ $-NH-C(=NH)-NH_2$	

Tables 2 and 3 or as a subgroup of the depolymerizable soluble polymers, which are described in Table 4. The solubilizable macromolecules can be insoluble calcium or magnesium salts of carboxylic or sulfonic acid bearing synthetic chains that undergo dissolution in the organism by cation exchange with alkalic metal salts. From this point on, the bioabsorption of these materials follows the same pattern as those noted for the water-soluble polymers. In addition, a solubilizable polymer can conceptually be a synthetic insoluble macromolecule that undergoes limited in-chain or side-chain scission to produce water-soluble, lower molecular weight fractions. For instance, a polyether–ester copolymer of polyethylene glycol diol with glycolic acid and/or an aliphatic diacid may undergo hydrolysis to a water-soluble polyethylene oxide and low molecular weight polyester fragments that undergo further hydrolysis to water-soluble monomeric species. The bioabsorbability of polymethyl cyanoacrylate may also in part be attributed to hydrolysis of the ester and/or the cyano group attached to the polyethylene main chain to create water-soluble polymeric moieties, which are transported and eliminated from the living organism earlier for intrinsically water-soluble polymers as discussed.

Depolymerizable Polymers

The third class of bioabsorbable polymers are those made of chains that undergo depolymerization to simple organic compounds in the living organism. The depolymerization may take place via an enzyme-catalyzed or chemicallyinduced scission of the polymer chains, as in the case of collagen or polyglycolic acid, respectively. Most, if not all, the enzymatically depolymerizable (or simply degradable) polymers are naturally occurring chains such as collagen or fermentation products, as in the case of poly-β-hydroxybutyric acid (PHB) (17). In addition, enzyme-degradable (or depolymerizable) polymers can be water-soluble (e.g., gelatin, pectin, hyaluronic acid, and protamine sulfate) or water-insoluble (e.g., collagen). A list of the water-soluble depolymerizable polymers is given in Table 4. Depending on their molecular weight, movement of the water-soluble polymers across the biologic membrane can take place by passive diffusion or endocytosis (or pinocytosis) as for low and high molecular weight chains, respectively. In most cases, however, water-soluble polymers undergo enzyme-catalyzed chain degradation to essentially monomeric species that can be metabolized further or excreted as such. The water-insoluble depolymerizable polymers are represented by three major naturally occurring polymers and derivatives thereof. The most common types of water-insoluble depolymerizable polymers are those based on natural proteins such as collagen and its derivatives (through complex formation with transition metals such as chromium ions). These are degraded by collagenase to soluble low molecular or monomeric species that may be excreted as such or metabolized further to ammonia water and carbon dioxide. Chitin, a polysaccharide, and its deacylated derivative, chitosan, represent the second important type of insoluble enzyme-degradable polymers. Poly-β-hydroxy-butyric acid and copolymers β-hydroxybutyric and β-hydroxyvaleric acid, which are fermentation products, represent the third type, the relatively new water-insoluble enzyme-depolymerizable polymers (see Table 5). The polysaccharide and polyester types of insoluble materials are likely to undergo enzyme

Table 5 Typical examples of natural enzyme depolymerizable waterinsoluble polymers

Polymer	Class of polymer or source	Special comments
Collagen	A protein, the main constituent of connective tissues and the organic component of bones	It contains high concentrations of glycine (33%) and proline (13%); it also contains hydroxyproline (10%) and the uncommon hydroxylysine (10%)
Chitin	A natural polysaccharide obtained from crab shells	The chain is based on acetylated glucosamine units; the natural polymer can be converted to the acid-soluble partially deacetylated product chitosan
Poly-β-hydroxybutyrate and copolymers	Aliphatic polyesters of 3-hydroxybutyric acid (HB) and copolymers of HB and 3-hydroxyvaleric acid (HV)	Prepared by fermentation; most polymers are crystalline thermoplastic film and fiber-forming materials and dissolve in certain organic solvents

degradation first to water-soluble low-molecular-weight or monomeric species for their transport across biologic membranes.

SYNTHETIC BIOCHEMICALLY ABSORBABLE POLYMERS

Until the late 1960s, collagen-based surgical products (mainly sutures) dominated the field of absorbable polymers. However, a few undesirable features associated with the natural origin of these products motivated the health care community to develop synthetic, absorbable polymers with more predictable and superior properties. In the past two decades, four major synthetic, biochemically absorbable polymers were introduced in the form of surgical sutures and allied surgical devices. These are polyglycolide (PGA); 90/10 poly(l-lactide-co-glycolide) (90/10 PLG); poly-*p*-dioxanone (PDS); and copolymers of polytrimethylene carbonate and glycolide (18–20). Other forms of lactide–glycolide copolymers and their blends have been converted to absorbable staples (21, 22). Although several forms of polylactides, including the optically pure poly-l-lactide, have been discussed extensively by many investigators (23, 25), their marketing as useful health-care products is hardly existent. A major potential use of these polymers is likely to be in the area of bone augmentation. The degradation of the lactide-glycolide systems and PDS was examined by a few authors (18, 26–28). Although the bioabsorption of these polymers is considered to be chemically driven, a few authors advocate that lactide-glycolide polymers (29, 30) and caprolactone polymers (31) undergo enzymatic degradation.

Synthetic bioabsorbable polymers other than those made mostly from glycolide, lactide, or *p*-dioxanone have been described in the technical and patent literature (18, 32–35). Dominant among these polymers are the polyoxalates (18, 34, 35), poly(carbalkoxyalkyl 2-cyanoacrylates) (36), polyanhydrides (37, 38), and absorbable organometallic or inorganic polymers such as polyphosphazenes (39) and phosphate glass as composites in absorbable organic matrices (40). Different types of polyalkylene oxalates and isomorphic copolyoxalates (based on 1,6-hexanediol and 1,4-*trans*-cyclohexanedimethanol) have been patented as useful bioabsorbable materials with tailored bioabsorption profiles, depending on their chemical structure, molecular weight, and morphology (34, 35). These polymers were noted as useful for the production of many surgical implants (including sutures) and surface lubricants. Polyanhydrides such as poly(trimethylene-bis-*p*-oxybenzoic anhydride), poly(terephthalic anhydride), and their copolymers with poly(sebacic anhydride) have been synthesized, and their degradation as bioabsorbable materials was studied by Leong and co-workers (37). These polymers were indicated to be nontoxic and nonmutagenic (38). Other polymers that have been described as bioabsorbable include copolymers of polytrimethylene malonate and *p*-dioxanone (41), polyalkylene oxamates (35), polyesteramides (42), poly-*p*-malolactone (43), copolymers of dl-lactide and ethylene oxide (44), copolymers of substituted glycolic acid and glycine (45), and polyorthoesters (46). Modulation of the properties of biochemically absorbable polymers to impart certain desirable properties has been achieved by Shalaby and his co-workers (18, 47, 48). To increase the bioabsorption of poly-*p*-dioxane, a small proportion of codimeric sequences based on morpholinedione were introduced into the polymer main chain (49). In order to improve the radiation stability of polyglycolide and poly-*p*-dioxanone, copolymers and/or melt-blends of these polymers with a polyester based on phenylene-diglycolic acid or carboxymethylated *p*-hydroxy benzoic acid were prepared and converted to radiation-sterilizable surgical articles (47, 48, 50–53). Typical examples of the biochemically absorbable polymers and an outline of their key properties and/or applications are given in Table 6. The newly developed class of absorbable gel-former polymers is addressed below.

ABSORBABLE GEL-FORMERS AND THEIR USE AS INJECTABLE CARRIERS

Growing interest in developing absorbable pharmaceutical surgical products that degrade in the biologic environment to safe byproducts and leave no residual mass at the application site (54–60), justified the search for novel, absorbable gels. In a recent disclosure (61), a novel gel-former was described to be based on absorbable copolymers which, upon hydration, result in hydrogels that are stabilized by pseudo-crosslinks provided by a hydrophobic polyester component covalently linked to a hydrophilic component made of pharmaceutically acceptable polymer, such as polyoxyethylene. The polyester component is made of safe monomers, such as *p*-dioxanone, ε-caprolactone, glycolide, lactide, and mixtures thereof. Contrary to a related study (62) that describes in situ formation of biodegradable, microporous, solid implants in a living body through coagulation of a

Table 6 Typical examples of waterinsoluble chemically depolymerizable polymers

General class	Specific examples	Key properties and/or applications[a]
Poly-2-hydroxy acids and copolymers	a. Polyglycolic acid (PGA)	A, B, F, G
	b. 10/90 l-lactide/glycolide copolymer (910 polyglactin)	A, B, F
	c. Poly-l-lactide	A, B, C, D, F, G
	d. Glycolide/ϵ-caprolactone copolymers	A, B, G, H, I
	e. Glycolide/1,5-dioxepan-2-one copolymers	A, B, G, H, I
	f. Glycolide/trimethylene carbonate copolymers	A, B, F, G
	g. Copolymers of glycolide and polyethylene-*p*-phenylene diglycolate	A, B, G, J
Poly-*p*-dioxanone and copolymers	a. Poly-*p*-dioxanone (PDS)	A, B, F, G
	b. Copolymers of PDS and l-lactide	A, B, G
	c. Copolymers of PDS and glycolide	A, B, G
	d. Poly-*p*-dioxanone-co-morpholine-2,5 dione	A, B, G
	e. Copolymers of *p*-dioxanone and polyethlyene-*p*-phenylene diglycolate	A, B, G, J
	f. Copolymers of polytrimethylene malonate and *p*-dioxanone	A, B, G, H
Polyalkylene oxalates	a. Polyesters of C4 to C16 and copolymers	A, B, C, D, E, G, H, I
	b. Isomorphic copolyoxalate of cyclic and alicyclic diols	A, B, C, D, G
Polyester-amides	Polyalkylene oxamate based on β-hydroxy-l-hexanol	A, B, G
Polyanhydrides	Copolyanhydrides of sebacic and 1,3-propane-bis-(4-oxybenzoate)	C, H

[a] A = Thermoplastic crystalline polymer; B = Melt processable into fibers and films; C = Soluble in certain common organic solvents; D = Film-former by solution dipping or casting; E = Low-Tm polymer (below 100°C); F = Used to produce surgical devices; G = Patented as useful polymers for surgical and allied devices; H = Described as useful matrices for drug delivery; I = Patented as a surface coating; J = Sterilizable by gamma radiation.

solution of a polymer in an organic solvent such as *N*-methyl-2-pyrrolidine, the new hydrogel-former does not require the use of solvents. Such solvents did include low molecular organic ones that can migrate from the application site and cause damage to living tissue, such as cell dehydration and necrosis. Equally important is the fact that previously known systems are solid implants that can elicit mechanical incompatibility and, hence, patient discomfort in contrast to the new compliant, swollen, mechanically compatible hydrogels (61).

The use of absorbable gel-formers may very well lead to some of the most important applications of absorbable polymers in the pharmaceutical and biomedical industries. Among the recent activities in this area are uses of the gel-formers in 1) periodontal application of antibiotics; 2) antibiotic formulations for osteomyelitis; 3) intraocular drug delivery; 4) wound healing and hemostasis; 5) controlling the release of insulin; 6) controlling the bioavailability of ricin A-chain; 7) wound repair as a suture adjuvant; 8) modifying absorbable tissue adhesives; 9) intravaginal controlled delivery of misoprostol; and 10) sealing microporous vascular grafts. These uses are discussed next.

Periodontal Application

This entails the use of injectable gel-forming formulations for controlled delivery of antibiotics, such as tetracycline or doxycycline, for combating periodontal infections for periods of 1–4 weeks (61).

Antibiotic Formulations for Bone Infection

In a Phase I study of an NIH-SBIR program addressing osteomyelitis, available results (63) indicate that 1) selected gel-formers are capable of controlling the in vitro release of gentamicin and vancomycin for at least 2 weeks; 2) two types of gel-formers can be formulated, with clinically relevant doses of vancomycin, into

injectable forms; 3) injection of the vancomycin formulation about the periosteum of the goat tibia for localized drug delivery; and 4) controlled release of the vancomycin formulation is feasible without leading to toxic blood levels.

Injectable Intraocular Delivery Systems

In an SBIR (Phase I) supported by the DOD, the feasibility of using tailored gel-formers to develop an injectable, controlled release system for intraocular delivery of key drugs is being investigated. The available data indicate that:

1. Injectable gel-formers containing pilocarpine, naproxen, cyclosporin, and ganciclovir in clinically relevant doses can be prepared.
2. A continued release in a buffered medium for at least one week can be achieved.
3. Active formulations of the four drugs and a placebo can be readily injected into the vitreous cavity of the rabbit eye without eliciting unacceptable, gross tissue reactions.

Burn Wound Healing and Hemostatic Application

Preliminary results of a study supported by a DOD grant on wound healing and hemostatic agents (using hairless rats and rabbits) indicate that:

1. Certain gel-forming formulations can be used for the controlled delivery of antibiotics to incisional and burn wounds in hairless rats.
2. Incisional wound repair in hairless rats can be improved when placebo gel-formers are used.
3. Selected gel-forming formulations can induce hemostasis in a rabbit animal model.

Insulin Controlled Release Systems

Preliminary study on the use of certain gel-formers for the controlled release of insulin demonstrates the feasibility of this concept (64).

Controlled Release of Ricin A-Chain and Other Vaccines

This has been the subject of a Phase I SBIR program supported by the DOD. Results and relevant conclusions of the study (65) are summarized below. Available results on subcutaneously (sc) administered active formulations do verify that:

1. Gel formulations can be easily prepared and appear suitable for scale-up.
2. One sc formulation is capable of releasing sufficient amounts of ricin A-chain (RAC) to elicit IgG formation at protective levels over a period of 4–6 weeks.
3. One formulation provides persistent protection for at least 6 weeks postimmunization.
4. A correlation can be established between IgG formation and the composition of the polymeric carriers.

Available Phase I results do not only fulfill these criteria but also suggest that:

1. A single-shot, absorbable sc formulation, GF-II, exhibits potentially unique in vivo performance as it comprises a microparticulate cation-exchanger.
2. Upon comparing commercial RAC solution (RAC-L) with GF-II, the latter elicits a more gradual antibody response that peaks at 10 weeks, and it exceeds a fast-decaying, initially higher response to RAC-L.
3. In terms of antibody response, GF-II is associated with higher durability over the 10 – 20 week period.
4. GF-II elicits a higher response of IgG-2A than RAC-L at 6 weeks.

Skin Wound Repair

In a study of skin wound repair, using sutures or staples on rats, it was shown that covering the wound with gel-formers allows the use of half the number of interrupted suture stitches or staples while minimizing scar formation.

Tissue Adhesive Formulation

The addition of certain members of the family of gel-formers to methoxypropyl cyanoacrylate yields a series of tissue adhesive formulations, which can be used a effectively as:

1. Sutures and staples in repairing skin wounds.
2. Affixing elastin-based patches in repairing defects at certain sties of the gastrointestinal tract.

Intravaginal Controlled Delivery of Misoprostol

In a recent study, gel-formers have shown to be effective carriers for the controlled release of misoprostol in a

newly developed animal model for studying induced cervical ripening.

Sealing of Microporous Vascular Grafts

The preliminary results of a recent study on expanded Teflon® vascular grafts show that certain gel-formers can be used as sealants for these microporous implants. As sealants, they can also be used as carriers for the controlled delivery of bioactive agents to prolong patency of the grafts.

REFERENCES

1. Molyneux, P. Br. Polym. J. **1986**, *18* (32).
2. Franz, G. Adv. Polym. Sci. **1986**, *76* (3).
3. Sakellariou, P.; Rowe, R.C.; White, E.E.T. Inter. J. Pharm. **1986**, *34* (93).
4. McCormick, C.L.; Blackman, K.P.; Elliott, D.L. Angew. Makromol. Chem. **1986**, *144* (87).
5. Dubin, P.L.; Strauss, U.P. J. Phys. Chem. **1973**, *77* (1427).
6. Dubin, E.L.; Strauss, U.E. Hypercoiling in Hydrophobic Polyacids. *Polyelectrolytes and Their Applications*; Rembaum, A., Selegny, E., Eds.; D. Reidel Pub. Co.: Holland, 1975; 3.
7. Pantar, A.V.; Rao, V.M.R. Makromol. Chem., Rapid Commun. **1986**, *7* (77).
8. Ross-Murphy, S.B.; McEvoy, H. Br. Polym. J. **1986**, *18* (2).
9. Burfillo, S.G.; Ogawa, T.J. Appl. Polym. Sci. **1986**, *32* (3783).
10. Barbucci, R.; Casolaro, M.; Nocentini, M.; Reginato, G. Makromol. Chem. **1986**, *187* (1953).
11. Kataoka, K.; Tsuruta, T. Makromol. Chem. **1980**, *181* (1363).
12. Salamone, J.C.; Mahmud, N.A.; Mahmud, M.U.; Nagabhushanam, T.; Watterson, A.C. Polymer **1982**, *23* (843).
13. Tsuchida, E.; Abe, K. Adv. Polym. Sci. **1982**, *45* (1).
14. Abe, K.; Senoh, S. J. Polym. Sci. Part A; Polym. Chem. **1986**, *24* (3461).
15. Saito, S. Coll. Surf. **1986**, *19* (351).
16. Drobnik, J.; Rypàtcek, E. Adv. Polym. Sci. **1984**, *57* (1).
17. Miller, N.D.; Williams, D.E. Biomaterials **1987**, *8* (129).
18. Shalaby, S.W. Fibrous Materials for Biomedical Applications. *High Technology Fibers*; Lewin, M., Preston, J., Eds.; Marcel Dekker, Inc.: New York, 1985; Ch. 3.
19. Doddi, N.; Versfelt, C.C.; Wasserman, D. US Patent (to ETHICON, Inc.) 4,052,988, 1980.
20. Katz, A.R.; Mukaherjee, D.P.; Kaganov, A.L.; Gordon, S. Surg. Gynecol. Obstet. **1985**, *161* (216).
21. Adzick, N.S.; Harrison, M.R.; Flake, A.W.; Glick, P.L.; Bottles, K. Surg. Forum **1985**, *36* (479).
22. Steckel, R.R.; Jann, H.W.; Kaplan, D.; Jakowski, R.M. Obstet. Gynecol. **1986**, *68* (40).
23. Leenslag, J.W.; Gogolewski, S.; Pennings, A.J. J. Appl. Polym. Sci. **1984**, *29* (2829).
24. Leenslag, J.W.; Pennings, A.J.; Bos, R.R.M.; Rozema, E.R.; Boering, G. Biomaterials **1987**, *8* (70).
25. Tune, D.C.; Rohovsky, M.W.; Jadhav, B.; Lehman, W.B.; Strongwater, A.; Kummer, E. Proceed. A. C. S. Div. Polym. Mater. Sci. Eng. **1986**, *53* (502).
26. Gupta, M.C.; Deshmukh, V.G. Polymer **1983**, *24* (827).
27. Chu, C.C.; Louie, M.J. Appl. Polym. Sci. **1985**, *30* (3133).
28. Pitt, C.G.; Gu, Z.W. J. Controlled Release **1987**, *4* (283).
29. Williams, D.E.; Chu, C.C. J. Biomed. Mater. Res. **1983**, *17* (1029).
30. Vainionpaa, S.; Kilpikari, J.; Liaho, J.; Helevirta, P.; Rokkanen, P.; Tormala, P. Biomaterials **1987**, *8* (46).
31. Pitt, C.G.; Hendren, R.W.; Schindler, A. J. Controlled Release **1984**, *1* (3).
32. Devi, K.S.; Vasudevan, E. J. Macromol. Sci. Rev. Macromol. Chem. Phys. **1985**, c-*25* (315).
33. Devi, K.S.; Sinha, J.M.; Vasudevan, P. Biomaterials **1986**, *7* (193).
34. Shalaby, S.W.; Jamiolkowski, D.D. US Patent (to ETHICON, Inc.) 4,140,678; 4,141,087, 1979.
35. Shalaby, S.W.; Jamiolkowski, D.D. US Patent (to ETHICON, Inc.) 4,205,399; 4,226,243, 1980.
36. Kronenthal, R.L.; Sehipper, E. US Patent (to ETHICON, Inc.) 3,995,641, 1976.
37. Leong, K.W.; Brott, B.C.; Langer, R. J. Biomed. Mater. Res. **1985**, *19* (194).
38. Leong, K.W.; Amore, P.D.; Marietta, M.; Langer, R. J. Biomed. Mater. Res. **1986**, *20* (51).
39. Allcock, H.R. Macromol. Chem., Macromol. Symp. **1986**, *6* (101).
40. Kronenthal, R.L. US Patent (to ETHICON, Inc.) 4,612,923, 1985.
41. Koelmel, D.E.; Shalaby, S.W. US Patent (to ETHICON, Inc.) 4,559,945, 1985.
42. Barrows, T.H.; Grussing, D.M.; Hegdahl, D.W. Trans. Soc. Biomater. **1983**, *6* (109).
43. Lenz, R.W.; Vert, M. US Patent 4,265,247, 1981.
44. Zhu, K.J.; Xiangzhou, L.; Shilin, Y. J. Polym. Sci., Part C, Polym. Lett. **1986**, *24* (331).
45. Goodman, M.; Kirshenbaum, G.S. US Patent (to Suture, Inc.) 3,773,737, 1973.
46. Choi, N.S. U.S. Pat. 4,093,709, 1978.
47. Bezwada, R.S.; Shalaby, S.W.; Kafrawy, A. Newman, H. US Patent (to ETHICON, Inc.) 4,643,191, 1987.
48. Bezwada, R.S.; Shalaby, S.W.; Newman, H. US Patent (to ETHICON, Inc.) 4,653,497, 1987.
49. Shalaby, S.W.; Koelmel, D.E. US Patent (to ETHICON, Inc.) 4,441,496, 1984.
50. Bezwada, R.S.; Shalaby, S.W.; Jamiolkowski, D.D. US Pat. (to ETHICON, Inc.) 4,510,295, 1985.
51. Koelmel, D.E.; Jamiolkowski, D.D.; Shalaby, S.W. US Patent (to ETHICON, Inc.) 4,546,152, 1985.

52. Koelmel, D.E.; Jamiolkowski, D.D.; Shalaby, S.W.; Bezwada, R.S. US Patent (to ETHICON, Inc.) 4,649,921, 1987.
53. Shalaby, S.W.; Jamiolkowski, D.D. US Pat. (to ETHICON, Inc.) 4,435,590, 1984.
54. Shalaby, S.W.; Thermoreversible Gels. *Water-Soluble Polymers*; ACS Symp. Ser. American Chemical Society: Washington, DC, 1991; 467, Ch. 33.
55. Shalaby, S.W. Polym. News **1991**, *16* (238).
56. Shalaby, S.W. J. Appl. Biomater. **1992**, *3* (73).
57. Shalaby, S.W., Ed. *Biomedical Polymers: Design to Degrade Systems* : Hanser Publ.: New York, 1994.
58. Shalaby, S.W. et al. *Polymers of Biological & Biomedical Significance*; ACS Symp. Ser. American Chemical Society: Washington DC, 1994; 540.
59. Shalaby, S.W. et al. Irish Patent (to Kinerton, Ltd.) S-61251, 1994.
60. Shalaby, S.W. Indian J. Tech. **1993**, *31* (464).
61. Shalaby, S.W. US Patent (to Poly-Med, Inc.) 5,610,052, 1997.
62. Dunn, R.L. et al. US Patent 4,938,763, 1990.
63. Corbett, J.T. et al. Trans. Soc. Biom. **1998**, *21* (341).
64. Corbett, J.T. Poly-Med. Internal Report, 1996.
65. Corbett, J.T. et al. Trans. Soc. Biom. **1997**, *20* (362).